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EXAMINER	
NICHOLS, CHRISTOPHER J	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 06/24/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/015,391	BAKER ET AL.	
	Examiner	Art Unit	
	Christopher J Nichols, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 December 2001*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28-47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 December 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments, and/or Claims

1. The Preliminary Amendment filed 12 December 2001 has been received and entered in full.

2. The Preliminary Amendment filed 23 April 2002 has been received and entered in full.

3. The Preliminary Amendment filed 9 September 2002 has been received and entered in full.

Specification

4. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code (pp. 304 line 5; pp. 305 line 23). See MPEP §608.01.

Oath/Declaration

5. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:
Non-initialed and/or non-dated alterations have been made to the oath or declaration (for Inventor Dan Eaton). See 37 CFR 1.52(c).

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims **28-47** are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific, substantial and credible asserted utility or a well-established utility.

7. The claims are directed to an isolated nucleic acid comprising the SEQ ID NO: 276 polynucleotide sequence, variants, derivatives, and fragments thereof. The specification discloses that the nucleic acid of the SEQ ID NO: 276 polynucleotide sequence encodes the protein of the SEQ ID NO: 277 amino acid sequence (therein notated as "PRO1317" and "DNA71166-1685"). The SEQ ID NO: 276 polynucleotide sequence encodes a protein that bears similarity to semaphorin as well as other proteins. The semaphorin class of protein is known in the art to be large and diverse and the Specification as filed does not identity which semaphorin is claimed or what the properties of the claimed invention are.

8. Adams *et al.* (June 1996) "A novel class of murine semaphorins with homology to thrombospondin is differentially expressed during early embryogenesis." Mech Dev. **57**(1): 33-45 teaches that in the developing embryo, growing axons encounter a vast diversity of molecules

in the extracellular matrix (ECM) and on the surface of cells. Many ECM and cell surface molecules have been shown to promote the growth of neurites or to provide favorable substrates for their extension. In addition, different families of proteins which can exert repulsive effects on growth cones. The vertebrate semaphorin (collapsin) gene family encodes at least one protein that acts as a repulsive signal for both sensory and sympathetic growth cones (pp. 33).

9. The first member of the semaphorin gene family to be identified was the grasshopper Fasciclin IV/Semaphorin I. Cloning of the chick *collapsin* cDNA (now called *collapsin-I)* revealed the presence of a conserved domain of 500 amino acids and 16 conserved cysteines in both proteins, which was named semaphorin domain. The high conservation of specific motifs in this domain allowed the isolation of a number of related genes both in invertebrates and vertebrates, including five new members of the semaphorin gene family (*semA-3*) from mouse (pp. 33; Figure 2). Comparison of their semaphorin domain sequences allowed the distinction of at least four different classes of semaphorin proteins, most of which contain a C2-type Ig-homology in addition to the semaphorin domain. So far only the invertebrate *semal* genes, which have a carboxy-terminal transmembrane sequence, lack this Ig motif.

10. The distribution of vertebrate semaphorin transcripts in mesodermal and neural tissues is highly complex (pp. 33; Figure 1). And the precise nature of their physiological effects may turn out to be determined not by a single domain, but by the integration of signals triggered by the activation of several receptors interacting with the different motifs present in the semaphorins. It also remains to be shown whether all these proteins function solely in axonal pathfinding or if they have more general roles (Figures 6 & 7). For example, semaphorins may represent extracellular signals regulating the cytoskeleton in various cell types and the repulsive effects of

Semaphorin D on sensory growth cones could represent just a special case. The isolation of a novel class of semaphorin with a potentially positively acting domain adds to this puzzle and highlights the complexity of this family of proteins (pp. 43). Thus the large diversity of the semaphorin gene family and the highly complex expression patterns of its individual members remain puzzling as long as more information from functional assays is lacking (pp. 43).

11. The instant specification discloses no data for any activity of the nucleic acid of the SEQ ID NO: 276 polynucleotide sequence encodes the protein of the SEQ ID NO: 277 amino acid sequence or any antibody specific for said protein. There are no working examples. There are no well-established utilities for newly discovered biological molecules. Applicant asserts numerous uses and includes a massive number of assays. However, the specification contains several assertions of utilities. For purposes of expedited examination, the Examiner will address only assays and uses directly applicable to the nucleic acid of the SEQ ID NO: 276 polynucleotide sequence encodes the protein of the SEQ ID NO: 277 amino acid sequence (therein notated as "PRO1317" and "DNA71166-1685"). Each of the relevant asserted utilities will be discussed in turn.

a. *The isolated nucleic acid of the SEQ ID NO: 276 polynucleotide sequence encodes a semaphorin protein of the polypeptide sequence of SEQ ID NO: 277:* The specification's assertion that the nucleic acid molecule of the SEQ ID NO: 276 polynucleotide sequence encodes a semaphorin protein of the polypeptide sequence of SEQ ID NO: 277 is credible but not specific or substantial. This assertion is based on sharing sequence homology with a least one known semaphorin protein. Püschel *et al.* (1995) "Murine semaphorin D/collapsin is a member of a diverse gene family and creates

domains inhibitory for axonal extension." Neuron **14**: 941-948 teaches a semaphorin protein that shares 81.4% sequence homology to the SEQ ID NO: 277 amino acid sequence (Figures 1 & 5). However, this assertion is not substantial as the sequence of semaphorins are diverse nor is it specific as their tissue distribution is greatly varied. Koppel *et al.* (September 1997) "A 70 Amino Acid Region within the Semaphorin Domain Activates Specific Cellular Response of Semaphorin Family Members." Neuron **19**(3): 531-537 teaches that the sequences of semaphorins are related but so divergent to give each one its own particular functional signaling activity (pp. 531). For example, although structurally similar Collapsin-1, Collapsin-2, Collapsin-3 (semaphorins) all have distinct activity (Figure 3). Therefore, the specification's assertion that the nucleic acid molecule of the SEQ ID NO: 276 polynucleotide sequence encodes a semaphorin protein of the polypeptide sequence of SEQ ID NO: 277 is not a substantial assertion of utility, since significant further research would be required of the skilled artisan to determine what its properties are. Nor is the assertion specific, as teaches the wide sequence variance and diverse tissue distribution of semaphorins.

b. *The isolated nucleic acid of the SEQ ID NO: 276 polynucleotide sequence encodes a semaphorin protein of the SEQ ID NO: 277 amino acid sequence has semaphorin biological activity*: This asserted utility is credible but not substantial nor specific because the art teaches that structural similarity in semaphorin proteins is not predictive of functional similarity. For instance, Luo *et al.* (June 1995) "A family of molecules related to collapsin in the embryonic chick nervous system." Neuron **14**(6): 1131-1140 teaches the discovery of four new molecules related to collapsin in chick

brains all of which contain a semaphorin domain named collapsin-2. It is structurally very similar to collapsin but is only 50% identical in its amino acid sequence and varies in its tissue expression distribution (Figures 1 & 2; pp. 1135-1136). In addition, function cannot be adequately predicted based solely on structural similarity to a protein found in the sequence databases. Thus one must be cautious in their use of sequence homology to assign a structure and function to a protein on sequence alone. Sequence homology is not a reliable as the sole basis upon which to establish biological activity. For example, Skolnick and Fetrow (2000) "From gene to protein structure and function: novel applications of computational approaches in the genomic era." Trends in Biotech. **18**(1): 34-39 state that knowing the protein structure by itself is insufficient to annotate a number of functional classes, and is also insufficient for annotating the specific details of protein function (see Box 2, p. 36). Similarly, Bork (2000) "Powers and Pitfalls in Sequence Analysis: The 70% Hurdle." Genome Research **10**:398-400 states that the error rate of functional annotations in the sequence database is considerable, making it even more difficult to infer correct function from a structural comparison of a new sequence with a sequence database (see especially p. 399). Such concerns are also echoed by Doerks *et al.* (June 1998) "Protein annotation: detective work for function prediction." Trends in Genetics **14**(6): 248-250 who state that (1) functional information is only partially annotated in the database, ignoring multi functionality, resulting in underpredictions of functionality of a new protein and (2) overpredictions of functionality occur because structural similarity often does not necessarily coincide with functional similarity. Smith and Zhang (November 1997) "The challenges of genome sequence

annotation or 'The devil is in the details'." Nature Biotechnology **15**:1222-1223 remarks that there are numerous cases in which proteins having very different functions share structural similarity due to evolution from a common ancestral gene. Brenner (April 1999) "Errors in genome annotation." Trends in Genetics **15**(4): 132-133 argues that accurate inference of function from homology must be a difficult problem since, assuming there are only about 1000 major gene superfamilies in nature, then most homologs must have different molecular and cellular functions. Finally, Bork and Bairoch (October 1996) "Go hunting in sequence databases but watch out for the traps." Trends in Genetics **12**(10): 425-427 add that the software robots that assign functions to new proteins often assign a function to a whole new protein based on structural similarity of a small domain of the new protein to a small domain of a known protein. Such questionable interpretations are written into the sequence database and are then considered facts. In any case, the art clearly shows that structural similarity of different semaphorin proteins is not predictive of expression patterns or functional similarity. Thus the specification's assertion that the polypeptide of the SEQ ID NO: 277 amino acid sequence encoded by the nucleic acid of the SEQ ID NO: 276 polynucleotide sequence has semaphorin activity is not a substantial assertion of utility, since significant further research would be required of the skilled artisan to determine what those activities are. Therefore while credible, this utility is neither substantial nor specific.

c. *The isolated nucleic acid of the SEQ ID NO: 276 polynucleotide sequence can be used as probe or primer:* This asserted utility is credible but not specific or substantial. The specification asserts that the claimed isolated nucleic acid, variants, and fragments

thereof are useful as probes to detect genes encoding the nucleic acid of the polynucleotide sequence of SEQ ID NO: 277, as primers or hybridization probes in screening libraries, to amplify corresponding gene fragments, to identify potential genetic disorders, in sequence arrays, to screen collections of genetic material from patients who have a particular medical condition, in restriction fragment length polymorphism (RFLP) screens, to screen a human genomic library using PCR and other methods, to search sequence databases, and to identify mutations associated with a particular disease. Since there is no substantial utility for the encoded polypeptide (the SEQ ID NO: 277 amino acid sequence), there is also no substantial utility for the nucleic acid probes to identify such or the claimed nucleic acids. As it would take significant further research to determine if the polynucleotide could be used as probes for any particular disease, mutation, or condition, since no nexus between any disease or condition and an alteration or mutation in the nucleic acid of the SEQ ID NO: 276 polynucleotide sequence expression levels or form (i.e. mutations) has been disclosed in the specification. Further, since all nucleic acids can be used as probes or primers, this asserted utility is not specific.

d. *The isolated nucleic acid of the SEQ ID NO: 276 polynucleotide sequence can be used to make inhibitory antisense or sense oligonucleotides:* Although credible, this asserted utility would only be substantial if the encoded polypeptide (the SEQ ID NO: 277 amino acid sequence) had a substantial utility. Otherwise, significant further research would be required of the skilled artisan to use the claimed nucleic acid to make antisense or sense oligonucleotides, since it is unclear when it would be desirable to use the

inhibitory antisense or double stranded oligonucleotides. In addition this utility is not specific as any nucleic acid can be used to make inhibitory antisense or sense oligonucleotides.

e. *The isolated nucleic acid of the SEQ ID NO: 276 polynucleotide sequence can be used in chromosome mapping:* This asserted utility is credible but not specific or substantial. In order to be useful as a chromosomal probe, the precise chromosomal map position must be disclosed. The Specification does not teach the chromosome location of the nucleic acid of the SEQ ID NO: 276 polynucleotide sequence. It is a credible assertion as Xiang *et al.* (15 February 1996) "Isolation of the human semaphorin III/F gene (SEMA3F) at chromosome 3p21, a region deleted in lung cancer." Genomics **32**(1): 39-48 teaches that small cell lung cancer (SCLC) has been correlated with a deletion in the short arm of chromosome 3, with the region 3p21 being lost from one homologue in almost all cases (pp. 39). Two SCLC cell lines, NCI-H470 and GLC-20, have homozygous deletions in 3p21, and these deletions overlap with a fragment of chromosome 3 that has tumor suppression activity *in vivo* (Figure 1). Isolated cDNA clones from this region that are homologous to the genes constituting the semaphorin family. The cDNA clone represents a novel human semaphorin, termed sema III/F (HGMW-approved symbol SEMA3F), which is expressed as a 3.8-kb transcript in a variety of cell lines and tissues. The punitive semaphorin homologue has characteristics of a secreted member of the semaphorin III family with 52% identity to mouse semaphorin E, 49% identity with chicken collapsin/semaphorin D, and 33% and 29% homology to *Drosophilae* I and II, respectively (pp. 41; Figures 2 & 3). Although there is

reduced expression of this gene in several SCLC lines, no mutations were found (pp. 45-46). To the contrary, in the instant Specification not chromosome location or specific disease state has been ascribed to the nucleic acid of the SEQ ID NO: 276 polynucleotide sequence which encodes the polypeptide of the SEQ ID NO: 277 amino acid sequence thus failing to support the asserted identity of the protein encoded by the SEQ ID NO: 276 polynucleotide sequence. In the instant application, substantial further research would be required for the skilled artisan to determine where this particular sequence is mapped in order to use the nucleic acid in the asserted utility as a chromosomal map probe. The asserted utility is also not specific, since the entire class of genes can be asserted to be used in this way.

f. *The isolated nucleic acid of the SEQ ID NO: 276 polynucleotide sequence can be used to make polypeptides for analysis of binding and/or interacting molecules:* This asserted utility is credible but not specific or substantial. The instant specification does not disclose any known function for the claimed nucleic acid (the SEQ ID NO: 276 polynucleotide sequence, the polypeptide encoded therein (the SEQ ID NO: 277 amino acid sequence) nor any disease state, toxin, or poison associated either. Therefore, it is not clear how the skilled artisan would use a polypeptide manufactured by this method, for analysis, characterization, or therapeutic uses. Since significant further research would be required to determine how to use the claimed nucleic acid, the asserted utility is not substantial. In addition, this utility assertion is not specific as it can be applied to any given nucleic acid.

g. *The isolated nucleic acid of the SEQ ID NO: 276 polynucleotide sequence can be used in making transgenic animals:* This asserted utility is credible but not specific or substantial. No phenotype has been disclosed for such transgenic animals. In the absence of such disclosure, the skilled artisan would have to experiment significantly in order to determine how the transgenic animals could be used. Therefore, the asserted utility is not substantial. Also, any nucleic acid can be used in this manner therefore the asserted utility is not specific either.

h. *The isolated nucleic acid of the SEQ ID NO: 276 polynucleotide sequence can be used in gene therapy methods:* This asserted utility is credible but not specific or substantial. The instant specification does not disclose any known disease state, toxin, or poison associated with the nucleic acid of the SEQ ID NO: 276 polynucleotide sequence. Therefore, it is not clear how the skilled artisan would use the gene therapy constructs made with the claimed nucleic acid for therapeutic uses. Since significant further research would be required to determine how to use the identified polynucleotide, the asserted utility is not substantial. In addition this utility is not specific as any nucleic acid can be used in such a manner.

i. *The isolated nucleic acid of the SEQ ID NO: 276 polynucleotide sequence can be expressed in cell lines:* This asserted utility is credible but not specific or substantial. The specification asserts that the claimed nucleic acid is useful for expression in cell lines. Since there is no substantial utility for the claimed nucleic acid or the encoded polypeptide therein, there is also no substantial utility for the transformed cell lines. It would take significant further research to determine if the transformed cells could be used

for particular purpose, since no nexus between a disease state, mutations, expression patterns, signaling pathways, and the nucleic acid of SEQ ID NO: 276 polynucleotide sequence have been disclosed in the specification. Further, since all nucleic acids can be used to transform cell lines, this asserted utility is not specific.

j. *The isolated nucleic acid of the SEQ ID NO: 276 polynucleotide sequence can be used to make chimeric proteins:* Although credible, this asserted utility is neither specific nor substantial. The instant specification does not disclose any known a disease state, mutations, expression patterns, activity, or signaling pathways associated with the nucleic acid of SEQ ID NO: 276 polynucleotide sequence. Therefore, it is not clear how the skilled artisan would use a chimeric polypeptide for therapeutic, diagnostic, or research uses. Since significant further research would be required to determine how to use the claimed chimeric polypeptide, the asserted utility is not substantial. In addition this utility is not specific as any nucleic acid molecule can be used in such a manner.

k. *The isolated nucleic acid of the SEQ ID NO: 276 polynucleotide sequence can be used in tissue typing:* This asserted utility is credible but not specific or substantial. The specification discloses that primary lung tumor cells expressed "elevated" levels of the nucleic acid of SEQ ID NO: 276 polynucleotide sequence. This expression level is not clearly defined in a clinical, biochemical, or diagnostic context and therefore is of dubious value. In view of the art, Furuyama *et al.* (27 December 1996) "Identification of a novel transmembrane semaphorin expressed on lymphocytes." JBC **271**(52): 33376-81 teaches that mouse semaphorin G (M-sema G) encodes a semaphorin domain comprising a single putative immunoglobulin-like domain, a transmembrane domain, and a

cytoplasmic domain. M-sema G is similar to M-sema, semB, and semC (semaphorins; pp. 33376). In contrast to the dominant expression of M-sema F mRNAs in the nervous tissues, M-sema G mRNAs are strongly expressed in lymphoid tissues, especially in the thymus, as well as in the nervous tissues (Figures 2, 3, & 5). Furuyama *et al.*'s results demonstrate that semaphorin is expressed on lymphocytes and suggest that semaphorins may play a role in the immune system, as well as in the nervous system. Thus this asserted utility is not substantial because a skilled artisan would be confronted by an undue experimentation burden to discern what tissues specifically express the claimed nucleic acid and what the relevance is. Nor is it specific because the identity of the type of lung cancer has not been identified nor the nucleic acid of the SEQ ID NO: 276 polynucleotide's role therein.

1. *The isolated nucleic acid of the SEQ ID NO: 276 polynucleotide sequence can be used in drug development (such as agonists and antagonists):* While credible, this asserted utility is not specific or substantial. In such methods, compounds are screened either physically or through computer modeling to determine their ability to bind to the target sequence. Compounds that have on or the other activity are then labeled as potential drugs. However, the instant specification does not disclose any specific disease state wherein there is a change in the SEQ ID NO: 276 polynucleotide sequence expression levels or forms (i.e., mutations). Therefore, in light of the absence of a clearly defined isoform and its ligand/metabolite/inhibitor properties, it is not clear how the skilled artisan would use a potential drug identified by this method. Since significant further research would be required to determine how to use the identified potential drugs,

the asserted utility is not substantial. In addition this utility is not specific as any nucleic acid can be used in such a manner.

12. Therefore, in the absence of a well-established utility, and the absence of a specific, substantial and credible asserted utility, the claimed invention lacks patentable utility under 35 U.S.C. § 101.

13. If Applicant can submit evidence (in the form of a declaration under 37 CFR §1.132 or post-filing date publications) supporting the specification's assertion that the nucleic acid molecule of the SEQ ID NO: 276 polynucleotide sequence which encodes the polypeptide of the SEQ ID NO: 277 amino acid sequence has a specific function similar to a known *semaphorin protein*, wherein the specific function was predicted by the specification as originally filed, such would be viewed favorably as evidence of patentable utility.

14. Claims **28-47** are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

15. Furthermore, claims **28-47** are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

16. The claims are drawn very broadly to an isolated nucleic acid comprising the SEQ ID NO: 276 polynucleotide sequence, variants, derivatives, and fragments thereof. The language of said claims encompasses sequence variants, fragments, chemical derivatives, fusion proteins, tagged proteins, and chimeric proteins encoded by the isolated nucleic acid.

17. The specification teaches that the nucleic acid of the SEQ ID NO: 276 polynucleotide sequence encodes the protein of the SEQ ID NO: 277 amino acid sequence (therein notated as "PRO1317" and "DNA71166-1685").

18. However, the specification fails to provide any guidance for the successful production, isolation, and characterization of isolated nucleic acid comprising the SEQ ID NO: 276 polynucleotide sequence or any variants, derivatives, and fragments thereof. And since resolution of the various complications in regards to predicting protein structure, function, and nature purely based on sequence prediction is highly unpredictable, one of skill in the art would have been unable to practice the invention without engaging in undue trial and error experimentation. In order to practice the invention using the specification and the state of the art as outlined below, the quantity of experimentation required to practice the invention as claimed would require the *de novo* production, isolation, and characterization the nucleic acid comprising the SEQ ID NO: 276 polynucleotide sequence, variants, derivatives, and fragments thereof to correlate with known semaphorin proteins. In the absence of any guidance from the specification, the amount of experimentation would be undue, and one would have been unable to practice the invention over the scope claimed.

19. Additionally, a person skilled in the art would recognize that predicting the efficacy of using sequence homology alone to predict the structure, nature, and function of the nucleic acid

comprising the SEQ ID NO: 276 polynucleotide sequence, variants, derivatives, and fragments thereof as highly problematic (see MPEP §2164.02). Thus, although the specification prophetically considers and discloses general methodologies of producing, isolating, and characterizing the nucleic acid comprising the SEQ ID NO: 276 polynucleotide sequence, variants, derivatives, and fragments thereof, such a disclosure would not be considered enabling since the state of protein biochemistry is highly unpredictable and complex. The factors listed below have been considered in the analysis of enablement [see MPEP §2164.01(a) and *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)]:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

20. The following references are cited herein to illustrate the state of the art of protein biochemistry.

21. On the breadth of the claims, Koppel *et al.* (September 1997) "A 70 amino acid region within the semaphorin domain activates specific cellular response of semaphorin family members." Neuron **19**(3):531-7 teaches that the semaphorin family contains secreted and transmembrane signaling proteins that function in the nervous, immune, and cardiovascular systems. Chick collapsin-1 is a repellent for specific growth cones. Two other secreted members of the semaphorin family, collapsin-2 and -3, are structurally similar to collapsin-1 but have different biological activities. Semaphorins contain a 500 amino acid family signature

semaphorin domain. The semaphorin domain of collapsin-1 is both necessary and sufficient for biological activity, the semaphorin domain contains a 70 amino acid region that specifies the biological activity of the three family members, and the positively charged carboxy terminus potentiates activity without affecting specificity. Semaphorins interact with their receptors through two independent binding sites: one that mediates the biological response and one that potentiates it. Thus as the claims as instantly presented do not specify which semaphorin is instantly claimed, nor what is its activity, and in view of Koppel *et al.* a large number of potential identities are possible.

22. On the nature of the invention, Klostermann *et al.* (27 March 1998) "The chemorepulsive activity of the axonal guidance signal semaphorin D requires dimerization." JBC **273**(13):7326-31 teaches that the axonal guidance signal semaphorin D is a member of a large family of proteins characterized by the presence of a highly conserved semaphorin domain of about 500 amino acids. Semaphorin (SemD) and semaphorin B (SemB) form homodimers linked by intermolecular disulfide bridges. In addition to the 95-kDa form of SemD (SemD(95k)), proteolytic processing of SemD creates a 65-kDa isoform (SemD(65k)) that lacks the 33-kDa carboxyl-terminal domain. Although SemD(95k) formed dimers, the removal of the carboxyl-terminal domain resulted in the dissociation of SemD homodimers to monomeric SemD(65k). Mutation of cysteine 723, one of four conserved cysteine residues in the 33-kDa fragment, revealed its requirement both for the dimerization of SemD and its chemorepulsive activity (Figure 5). Thus dimerization is a general feature of semaphorins which depends on class-specific sequences and is important for their function. No such guidance is present in the instant Specification. Thus the skilled artisan is left to experiment and determine whether or not

dimerization is required and which residues are required for function of the instantly claimed protein.

23. On the existence of working examples, Encinas *et al.* (2 March 1999) "Cloning, expression, and genetic mapping of Sema W, a member of the semaphorin family." PNAS USA **96**(5): 2491-6 teaches that the semaphorins comprise a large family of membrane-bound and secreted proteins, some of which have been shown to function in axon guidance. Sema W, belongs to the class IV subgroup of the semaphorin family. The mouse and rat forms of Sema W show 97% amino acid sequence identity with each other, and each shows about 91% identity with the human form. The gene for Sema W is divided into 15 exons, up to 4 of which are absent in the human cDNAs that we sequenced. Unlike many other semaphorins, Sema W is expressed at low levels in the developing embryo but was found to be expressed at high levels in the adult central nervous system and lung (Figure 2). Functional studies with purified membrane fractions from COS7 cells transfected with a Sema W expression plasmid showed that Sema W has growth-cone collapse activity against retinal ganglion-cell axons, indicating that vertebrate transmembrane semaphorins, like secreted semaphorins, can collapse growth cones (Figure 5). Genetic mapping of human SEMAW with human/hamster radiation hybrids localized the gene to chromosome 2p13. Genetic mapping of mouse Sema W with mouse/hamster radiation hybrids localized the gene to chromosome 6, and physical mapping placed the gene on bacteria artificial chromosomes carrying microsatellite markers D6Mit70 and D6Mit189 (Figure 4). This localization places Sema W within the locus for motor neuron degeneration 2, making it a valid candidate gene for this disease. In contrast, none such work has been done to characterize and explain how to use the instantly claimed nucleic acid.

24. Regarding derivatives and fragments of isolated nucleic acid comprising the SEQ ID NO: 276 polynucleotide sequence, variants, derivatives, and fragments thereof and the polypeptides encoded therein, the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions [see Wells (18 September 1990) "Additivity of Mutational Effects in Proteins." Biochemistry **29**(37): 8509-8517; Ngo *et al.* (2 March 1995) "The Protein Folding Problem and Tertiary Structure Prediction, Chapter 14: Computational Complexity Protein Structure Prediction, and the Levinthal Paradox" pp. 433-506]. However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active muteins, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further

experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone [Bork (2000) "Powers and Pitfalls in Sequence Analysis: The 70% Hurdle." Genome Research **10**:398-400; Skolnick and Fetrow (2000) "From gene to protein structure and function: novel applications of computational approaches in the genomic era." Trends in Biotech. **18**(1): 34-39, especially p. 36 at Box 2; Doerks *et al.* (June 1998) "Protein annotation: detective work for function prediction." Trends in Genetics **14**(6): 248-250; Smith and Zhang (November 1997) "The challenges of genome sequence annotation or 'The devil is in the details'." Nature Biotechnology **15**:1222-1223; Brenner (April 1999) "Errors in genome annotation." Trends in Genetics **15**(4): 132-133; Bork and Bairoch (October 1996) "Go hunting in sequence databases but watch out for the traps." Trends in Genetics **12**(10): 425-427]. Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

25. Thus the specification of the instant application fails to provide adequate guidance for one of skill in the art to overcome the unpredictability and challenges of applying results from *sequence homology predictions* to the actual structure, function, and nature of the nucleic acid comprising the SEQ ID NO: 276 polynucleotide sequence, variants, derivatives, and fragments thereof as exemplified in the references herein.

26. Claims **28-47** are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The specification does not contain a written description of variants and fragments of the claimed semaphorin polypeptide.

27. *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

28. With the exception of the nucleic acid of the SEQ ID NO: 276 polynucleotide sequence, the skilled artisan cannot envision the detailed chemical structure of the encompassed polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a

potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

29. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

30. Therefore, only isolated polypeptides comprising the *nucleic acid* sequence set forth in SEQ ID NO: 276, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

31. Claims **28-33, 35-37,** and **41** are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

32. The claims recite "the extracellular domain" (e.g. claim 28, part c). The Specification does not clearly indicated where the extracellular domain is. See Figure 158, which indicates the presence of several punative transmembrane domains thus implying several extracellular domains.

33. Also the claims recite "the extracellular domain lacking its associated signal peptide". The art recognizes that full-length, secreted proteins often have signal peptides that are cleaved

during processing. However, such signal peptides are not known to be associated with "domains" of a full-length protein such as an extracellular domain.

34. Claims **41-43** are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

35. The term "stringency" in claim 42 is a relative term which renders the claim indefinite. The term "stringency" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

36. To satisfy the requirements of 35 U.S.C. §112 ¶2 Applicant must unambiguously define the limitations of the claims. "Stringent conditions" for hybridization, while known the art, are not unambiguously defined. A great deal of latitude and a range of conditions may be construed as "stringent". Also, stringency may be low, moderate, or high, none of which is specified by the claims as instantly neither presented nor supported by the Specification. For instance, the Roche website defines hybridization conditions under four parameters: temperature, pH, concentration of monovalent cations, and the presence of organic solvents, none of which are defined by the claims or the Specification ("Nucleic Acid Hybridization- General Aspects" pp. 33-37 Roche website retrieved on 12 May 2004). Also the NIH Division of Intramural Research teaches that "Nucleic Acid Hybridization" conditions vary. For temperature it teaches that it may be 25oC below duplex melting temperature, which varies due to the length of the polynucleotide and the GC content. Also, salt concentrations may vary between 5 to 6x SCC and denaturing agents such

a formamide ranges from 1% to 50% (NIH Division of Intramural Research "Nucleic Acid Hybridization" retrieved from NIH website on 12 May 2004).

37. Futhermore Umansky *et al.* US 6,287,820 states:

> Numerous equivalent conditions can be employed to comprise either low or high stringency conditions; factors such as the length and nature (DNA, RNA, base composition) of the probe and nature of the target (DNA, RNA, base composition, present in solution or immobilized, etc.) and the concentration of the salts and other components (e.g., the presence or absence of formamide, dextran sulfate, polyethylene glycol) are considered and the hybridization solution can be varied to generate conditions of either low or high stringency hybridization different from, but equivalent to, the above listed conditions. The term "hybridization" as used herein includes "any process by which a strand of nucleic acid joins with a complementary strand through base pairing".
>
> "Stringency " typically occurs in a range from about Tm-5°C. (5°C below the T_m of the probe) to about 20°C to 25°C below T_m. As will be understood by those of skill in the art, a stringent hybridization can be used to identify or detect identical polynucleotide sequences or to identify or detect similar or related polynucleotide sequences.

38. Therefore, stringent hybridization can be used to detect similar or related polynucleotide sequences, but there is no definite limit as to how similar or related the polynucleotide sequences have to be, and the claims are indefinite.

39. Therefore the skilled artisan is not apprised of the metes and bounds of what constitutes "stringent conditions". Neither the specification nor the art defines the term unambiguously. Thus the metes and bounds of the claims cannot be determined. Incorporation of those conditions which Applicant feels defines the term "stringent conditions" into the claims would obviate the rejection.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

40. Claims **28-43** are rejected under 35 U.S.C. 102(a) as being anticipated by WO 00/77239 (McCarthy *et al.*) 21 December 2000.

41. WO 00/77239 teaches a polypeptide that shares 100% sequence homology with the polypeptide of the SEQ ID NO: 277 amino acid sequence and nucleic acids thereof (Claim 8; Figures 1-3).

42. Since the claimed invention does not have an established or well-asserted utility, the instant Application is not entitled to any priority claims. Thus for purposes of art rejections the filing date of the instant application is 7 December 2001 (until utility is established) [see MPEP §].

Summary

43. No claims are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Christopher James Nichols, Ph.D.** whose telephone number is **(571) 272-0889**. The examiner can normally be reached on Monday through Friday, 8:00 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Gary Kunz, Ph.D.** can be reached on **(571) 272-0887**.

The fax number for the organization where this application or proceeding is assigned is **703-872-9306**.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see **http://pair-direct.uspto.gov**. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at **866-217-9197** (toll-free).

Elizabeth C. Kemmerer

CJN
June 16, 2004

ELIZABETH KEMMERER
PRIMARY EXAMINER